
بسم الله الرحمن الرحیم

Adverse Effects of Antiresorptive Therapy

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Disclosure


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Goals

1. Introduction
2. Common Adverse Effects
   . Gastrointestinal Effects of Oral Bisphosphonates
   . Acute Phase Reaction Following Intravenous Bisphosphonates
   . Hypocalcemia Associated with Antiresorptive Therapy
   . Bone, Joint, and Muscle Pain
3. Rare but Serious Adverse Effects
   . Atypical Femoral Fractures (AFF)
   . Osteonecrosis of the Jaw (ONJ)
4. Other Adverse Effects
   . Ocular Effects
   . Renal Toxicity
   . Rebound Bone Loss After Denosumab Discontinuation
   . Cardiovascular Events
   . Infection Risk
5. Risk Factors and Prevention Strategies
6. Comparative Frequencies and Severity
7. Conclusion and Implications

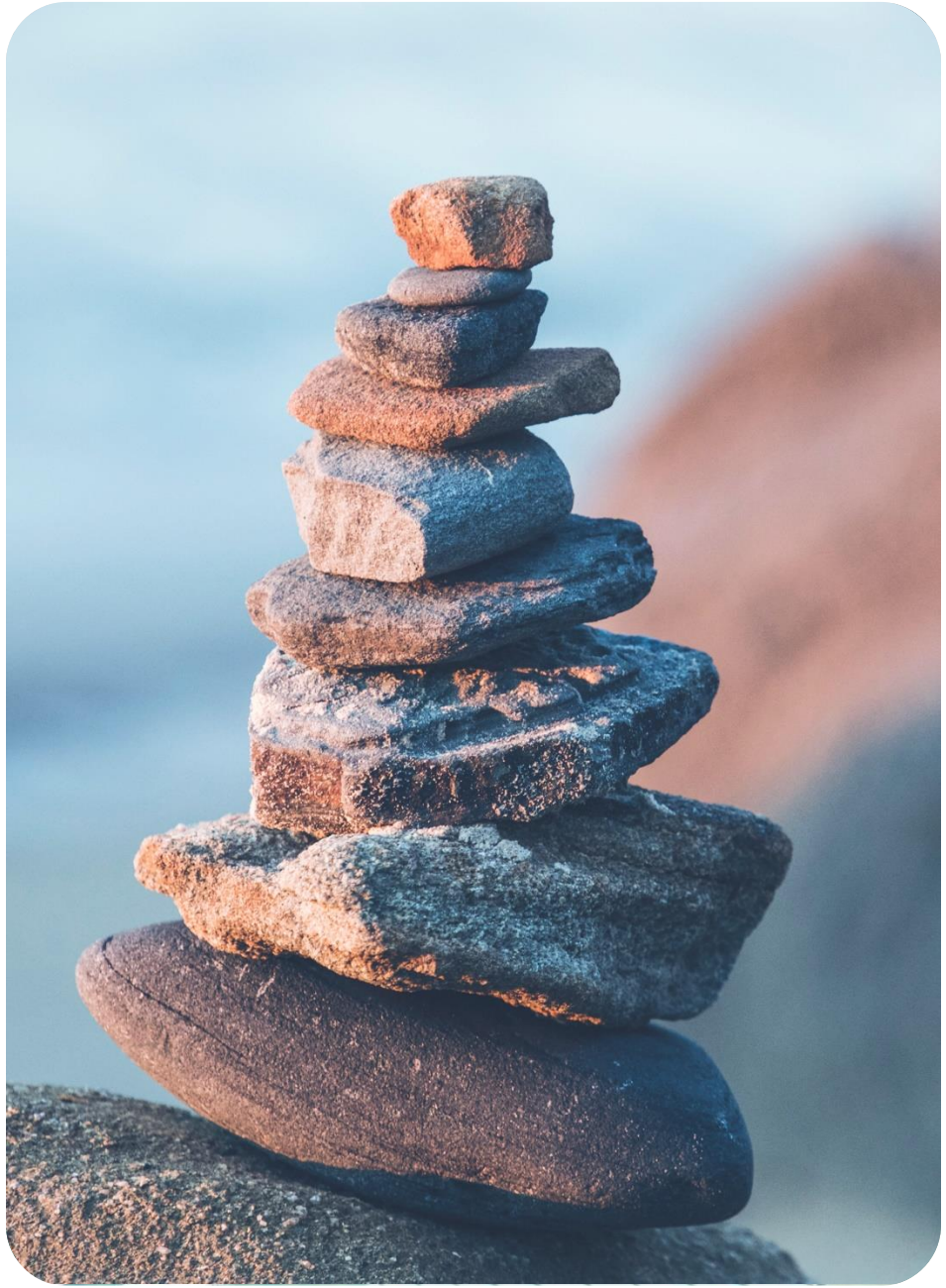
Introduction

Antiresorptive therapies have become a cornerstone in the management of osteoporosis and metastatic bone disease.

These drugs, including bisphosphonates and denosumab.

Bisphosphonates are a first-line pharmacological treatment for people at high risk of fracture.

Their mechanism of action, which involves the suppression of osteoclast-mediated bone turnover, is associated with a wide spectrum of adverse effects..



Common Adverse Effects

Gastrointestinal Effects of Oral Bisphosphonates

Acute Phase Reaction Following Intravenous Bisphosphonates

Hypocalcemia Associated with Antiresorptive Therapy

Bone, Joint, and Muscle Pain

Gastrointestinal Effects of Oral Bisphosphonates

Upper GI discomfort 20–30%

Reflux, esophagitis, and in some cases, the development of gastric or esophageal ulcers.

Other reported GI adverse 5%

Abdominal pain, diarrhea, and constipation.

Acute Phase Reaction Following Intravenous Bisphosphonates

Intravenous bisphosphonates, such as zoledronic acid

These formulations are associated with an infusion-related acute phase reaction.

This reaction typically presents as flu-like symptoms—including fever, chills, headache, myalgia, and arthralgia—occurring within the first 1 to 3 days after infusion.

Initial infusion approximately 30%

Subsequent infusions, less than 7%

Bone, Joint, and Muscle Pain

Less than 5%

Complaints of bone, joint, and muscle pain are infrequent.

These symptoms, which include skeletal discomfort, myalgia, arthralgia, and back pain, are generally described as mild to moderate in intensity.

The severity of pain can be more pronounced, particularly in the context of breast cancer treatment

Rare but Serious Adverse Effects

Atypical Femoral Fractures (AFF)

Osteonecrosis of the Jaw (ONJ)

Other Adverse Effects

Ocular Effects 1%

Renal Toxicity ?%

Rebound Bone Loss After Denosumab Discontinuation

Cardiovascular Events ?%

Infection Risk LOW%

Ocular Effects 1%

Ocular adverse effects

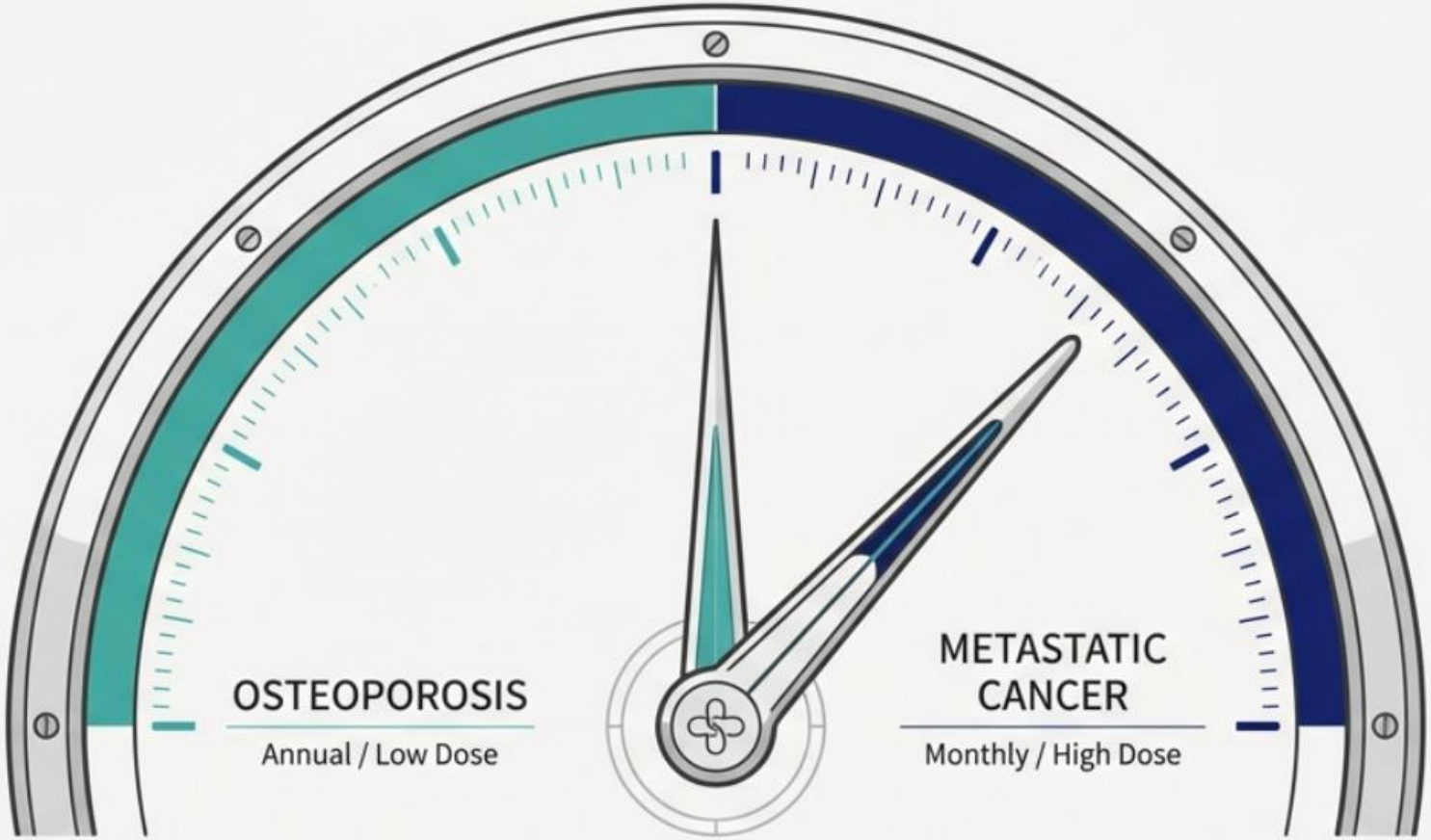
- Uveitis
- Conjunctivitis
- Scleritis

have been reported in patients treated with bisphosphonates.

Although these effects are rare, they are clinically significant due to the potential for impaired vision and discomfort .

Dose is Destiny

The Two Worlds of Antiresorptive Therapy

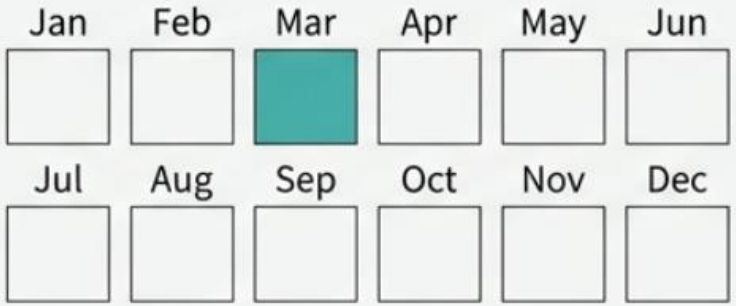


Understanding how the same drug class—bisphosphonates and denosumab—creates two vastly different risk profiles based on indication and dosing.

The 12x Difference in Cumulative Dose

Low-Dose Therapy

Zoledronic acid 5 mg **once a year**



High-Dose Therapy

Zoledronic acid 4 mg **every 3–4 weeks**

Cancer patients receive approximately **10–12 times the cumulative annual dose**, fundamentally altering the risk-benefit equation.

The Chasm of Risk: A Tale of Two Populations

	Osteoporosis (Low-Dose Therapy)	Cancer (High-Dose Therapy)
MRONJ	Very Rare (~0.01%) 	Common (1–15%) 
Hypocalcemia	Rare / Mild 	Frequent / Severe 
AFF	Very Rare Risk increases after 5+ years.	Rare Risk threshold reached faster due to high cumulative dose.
Renal Toxicity	Low Risk	Moderate Risk / Requires Monitoring

Summary of Key Complications by Patient Population

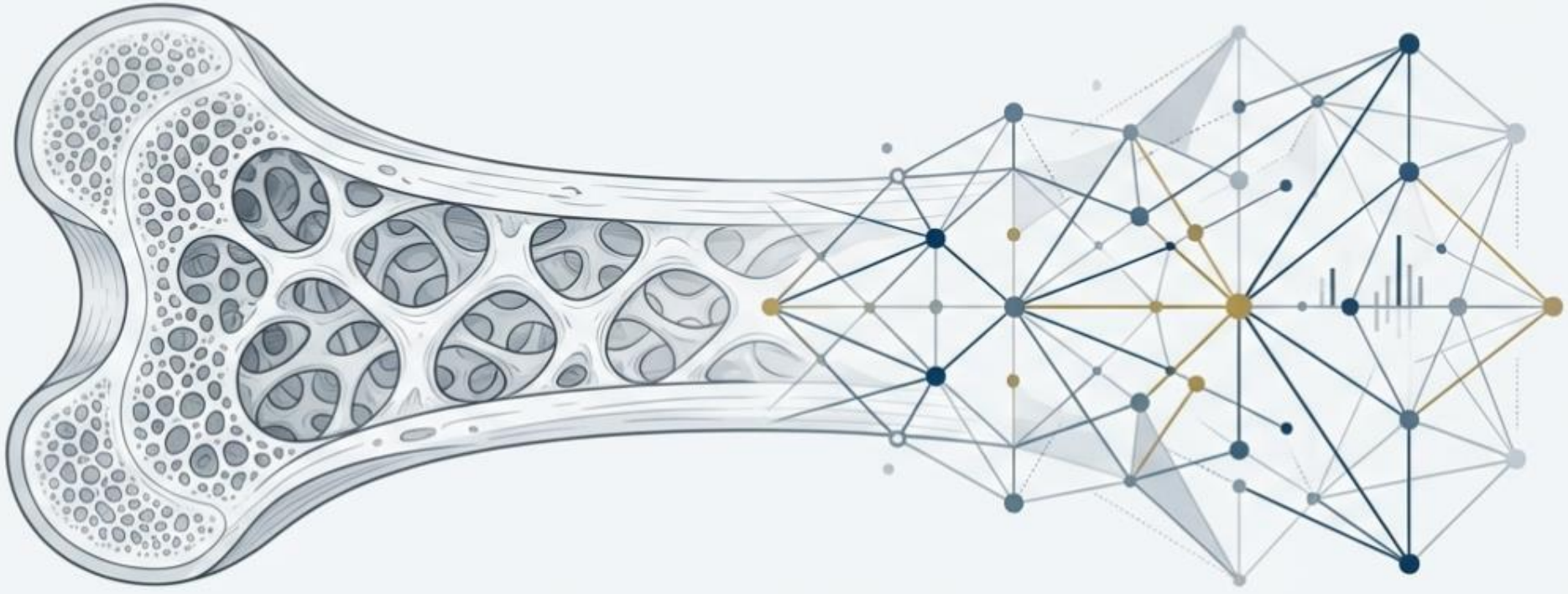
Complication	Osteoporosis (Low Dose)	Metastatic Bone Cancer (High Dose)
 **Osteonecrosis of the Jaw (MRONJ)**	**Very Rare** (~0.01% – 0.1%)	**Common** (1% – 15%)
 **Hypocalcemia**	**Rare** (usually mild)	**Frequent** (can be severe)
 **Atypical Femoral Fracture (AFF)**	**Very Rare** (risk increases after 5+ yrs)	**Rare** (risk accumulates faster)
 **Renal Toxicity** (Bisphosphonates)	**Low Risk**	**Moderate Risk** (requires monitoring)
 **Rebound Vertebral Fractures** (Denosumab)	**High Risk** (if stopped)	**Risk exists** (if interrupted)

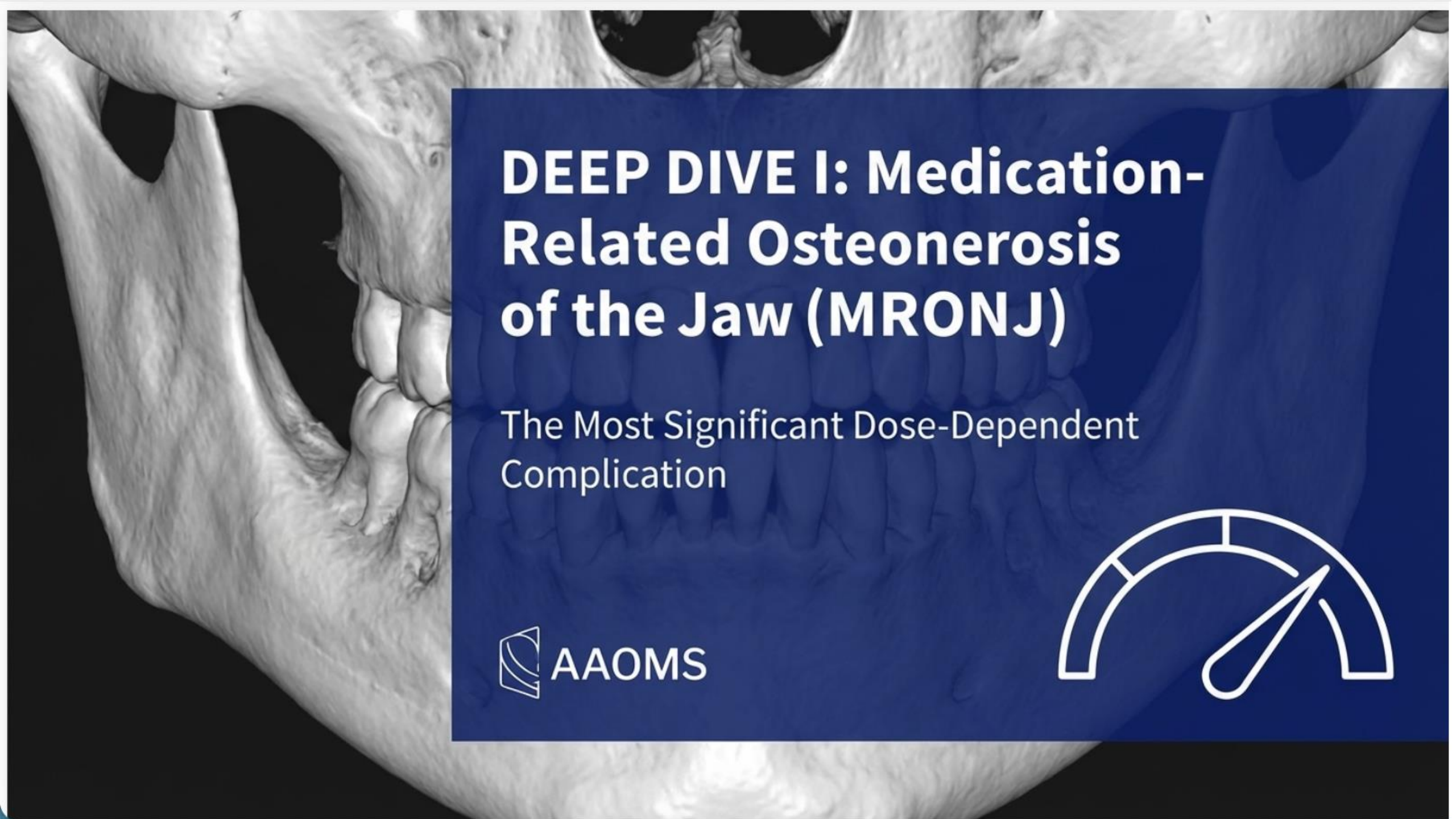
THE BALANCING ACT

Navigating the Risks of Antiresorptive Therapy:
A 2025 Clinical Update on AFF & MRONJ

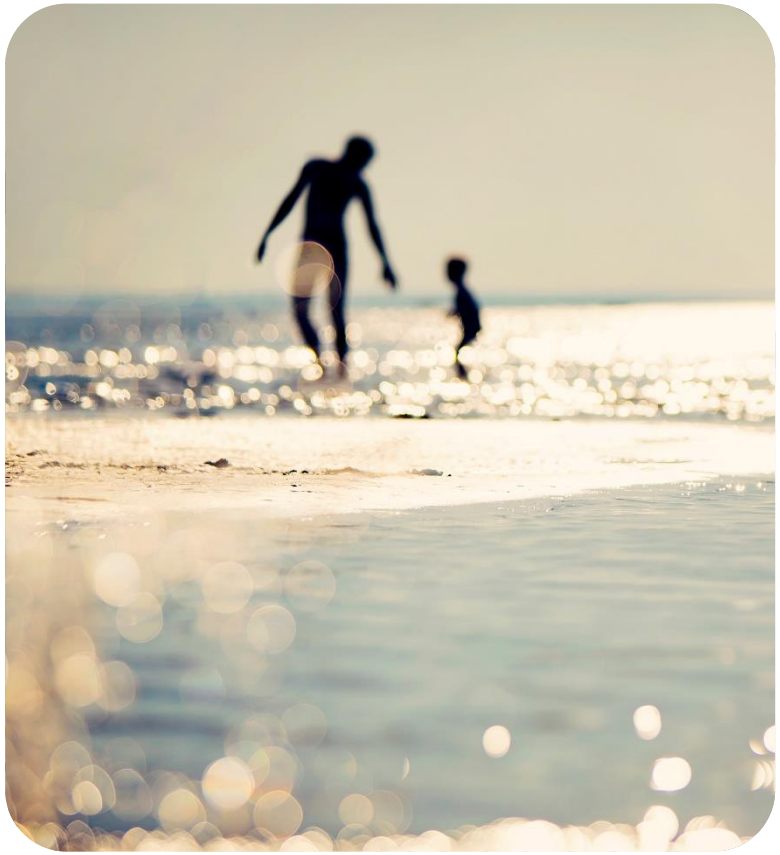
Managing Rare Adverse Events in Osteoporosis Therapy: A 2025 Clinical Synthesis

An Evidence-Based Briefing on Atypical Femoral Fracture and Medication-Related Osteonecrosis of the Jaw




DEEP DIVE I: Medication-Related Osteonerosis of the Jaw (MRONJ)
The Most Significant Dose-Dependent Complication
AAOMS

Osteonecrosis of the Jaw (ONJ)



Osteonecrosis of the jaw is among the most serious complications associated with antiresorptive therapy.

ONJ is relatively *rare* in patients receiving low-dose bisphosphonates for osteoporosis.

ONJ is *higher* in *cancer* patients receiving high-dose intravenous formulations.

- *Approximately 90% of the reported cases occur in the latter group*

Risk factors for *ONJ* include:

- dental extractions
- pre-existing dental disease
- the use of glucocorticoids
- diabetes
- smoking

MRONJ: Understanding the Condition and Stratifying Patient Risk

Definition & Diagnosis

AAOMS 2022 mamaiists definition: “Exposed bone, or bone that can be probed through an intraoral or extraoral fistula, in the maxillofacial region that has persisted for more than 8 weeks in a patient with a history of treatment with an antiresorptive or antiangiogenic agent, and who has no history of radiation therapy to the jaws.”

Key Risk Factors

- **Drug-Related**
  - Potency: IV Bisphosphonates > Oral Bisphosphonates > Denosumab
  - Duration of Therapy: >4 years significantly increases risk

- **Local Factors**
  - Dentoalveolar surgery (e.g., extractions)
  - Pre-existing periodontal or periapical disease
  - Poorly fitting dentures causing mucosal trauma

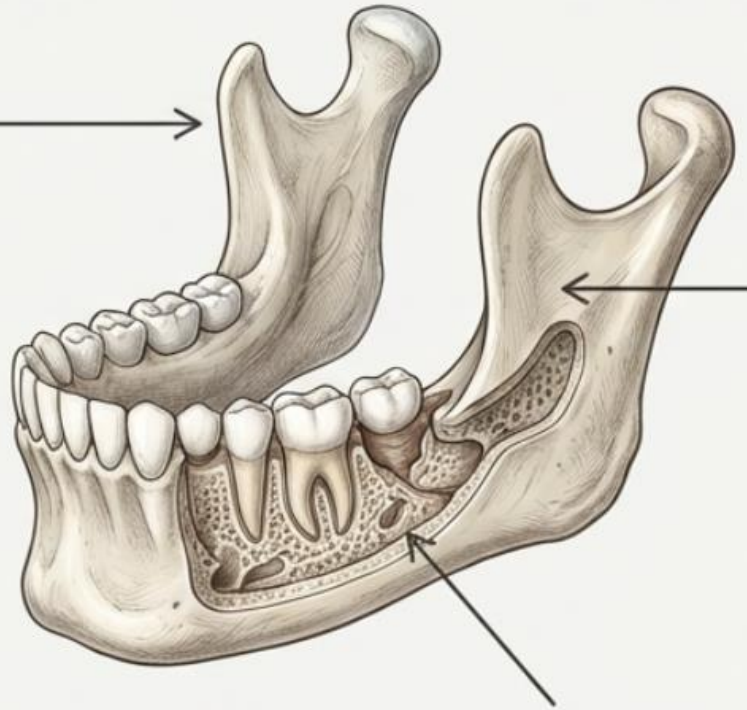
- **Systemic Factors**
  - Concurrent glucocorticoid use
  - Diabetes Mellitus
  - Smoking
  - Underlying cancer diagnosis

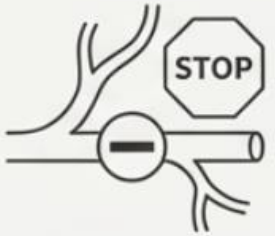
Risk factor synthesis from *AAOMS 2022 Position Paper* and *MRONJ Narrative Review (2023)*.

The Mechanism of MRONJ: Why the Jaw Fails

“Frozen” Remodeling

High-dose therapy halts the constant repair of micro-damage from chewing, leading to an accumulation of necrotic (dead) bone.





Inhibited Angiogenesis

Bisphosphonates prevent new blood vessel formation. When gums are breached, the underlying bone cannot vascularize to heal.

Bacterial Colonization

Exposed, non-vascular bone becomes a perfect surface for oral bacteria. The immune system cannot reach the infection, creating a vicious cycle.

Deep Dive: Osteonecrosis of the Jaw (MRONJ)

Mechanism: High-Dose Therapy Overwhelms the Jaw's Healing Capacity

High-dose therapy profoundly suppresses bone remodeling, preventing the jaw from healing daily micro-damage caused by chewing and dental procedures.
Tooth extraction is the trigger in ~60% of MRONJ cases.

Routine Care is Sufficient

The risk is only slightly higher than in the general population. Routine dental clearance before starting therapy is generally not required.
Good oral hygiene is always encouraged.

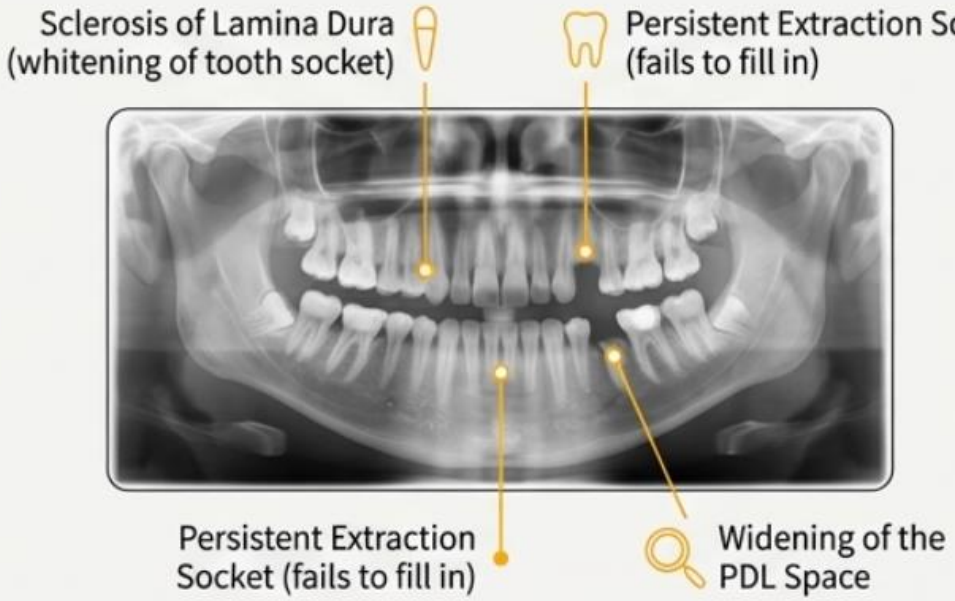
Proactive Prevention is Mandatory

Patients require a **comprehensive dental exam** and completion of **all invasive dental work** (extractions, implants) *before* initiating high-dose therapy.

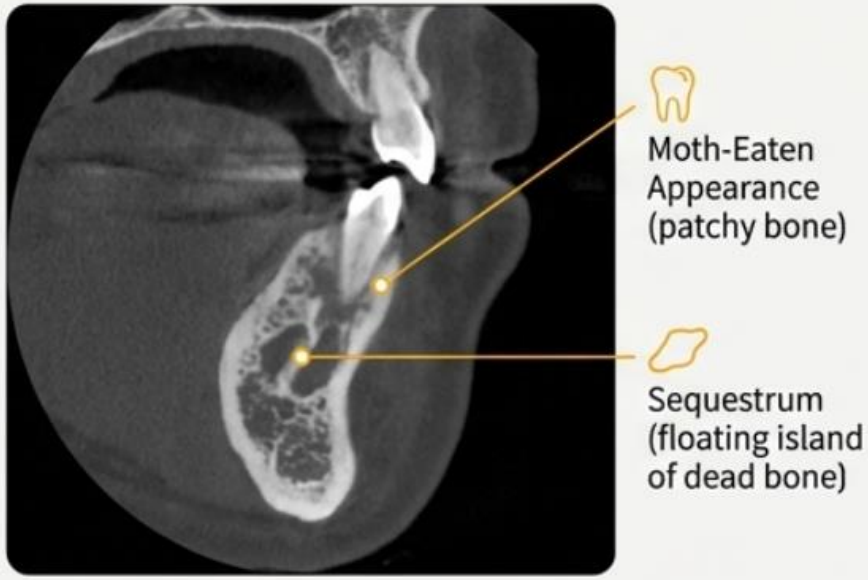
Reading the Signs: Imaging Findings in MRONJ

In early stages, patients may have severe pain with NORMAL X-rays.

Early Signs (High Index of Suspicion)



Advanced Signs (Established Necrosis)



Pro-Tip: Source Sans Pro Regular
Preferred Modality: **Cone Beam CT (CBCT)** is superior for defining the true extent of necrotic bone.

Clinical Pearl: Before High-Dose Therapy, a Dental ‘All Clear’ is Essential.

For any patient starting a high-dose antiresorptive regimen for cancer, the highest yield preventative strategy is a **pre-therapy dental evaluation** to address any potential sites of infection or areas requiring invasive procedures.

This single step can significantly reduce the risk of MRONJ.

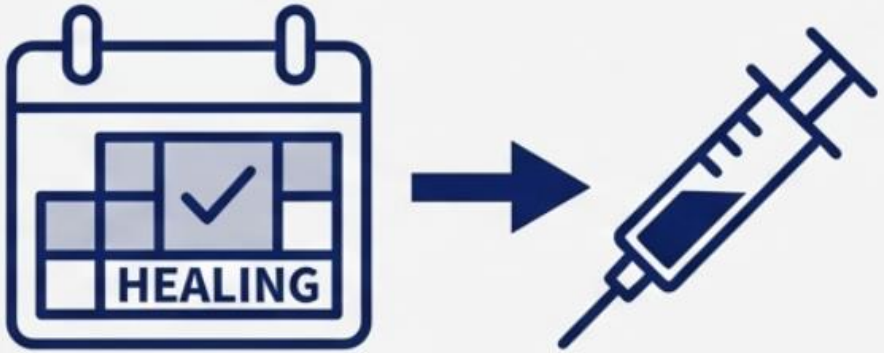
Authoritative Guideline: AAOMS Position Paper on Medication-Related Osteonecrosis of the Jaw – 2022 Update.

The Prevention Playbook: A Tale of Two Mandates

Osteoporosis / Low Dose
Routine Dental Care

Routine dental clearance is generally **not required** before starting therapy. Good oral hygiene is always encouraged.

Metastatic Cancer / High Dose
Mandatory Pre-Therapy Clearance

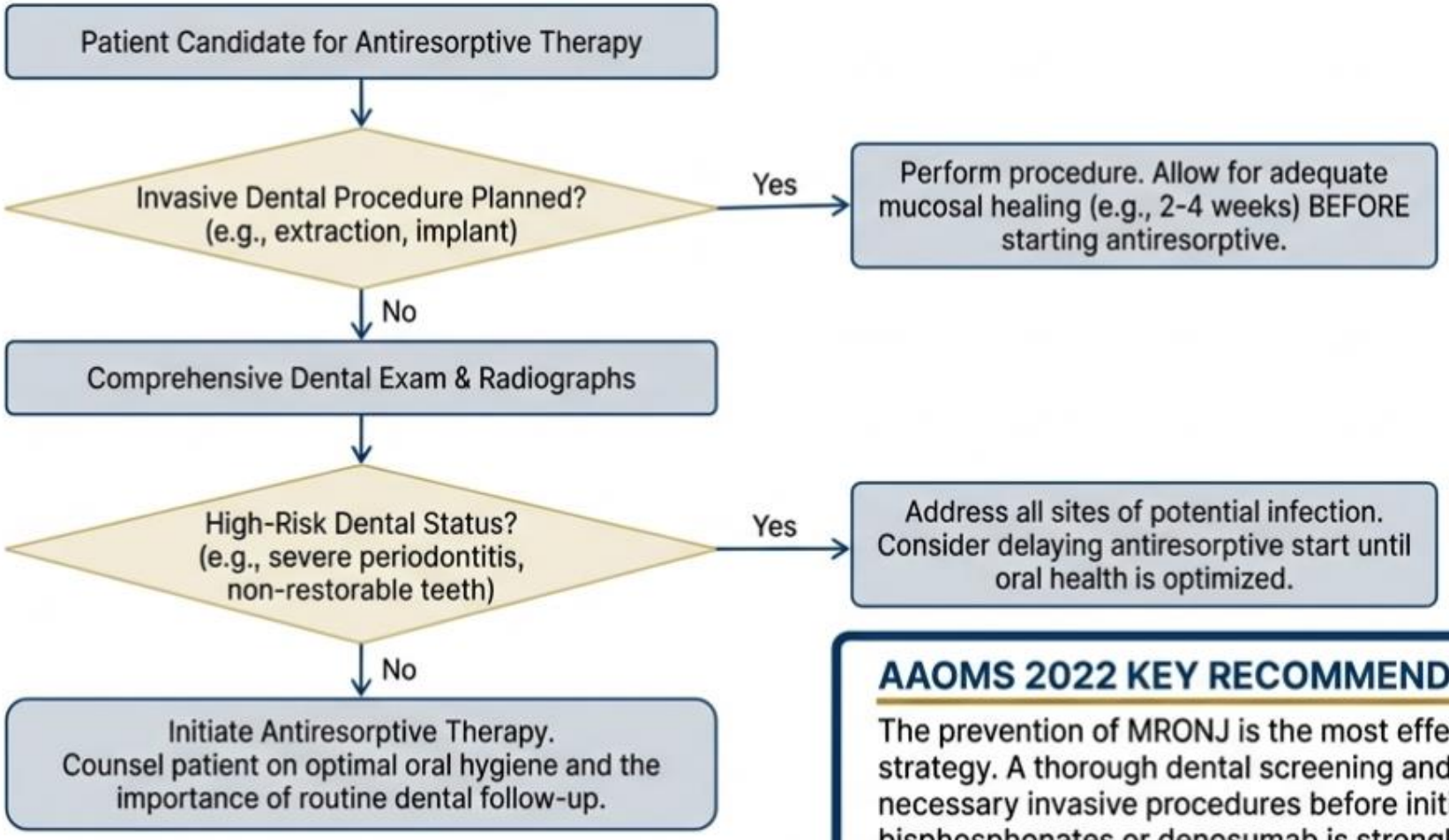


A comprehensive dental exam is **ESSENTIAL**. Extract all hopeless teeth and allow **full mucosal healing (14–21 days)** *before* the first drug infusion.

Guideline Update: The AAOMS **does not support** using serum CTX testing to predict MRONJ risk.

A Proactive Strategy for MRONJ Prevention Before Starting Therapy

Pre-Antiresorptive Dental Clearance Protocol



AAOMS 2022 KEY RECOMMENDATION

The prevention of MRONJ is the most effective management strategy. A thorough dental screening and completion of necessary invasive procedures before initiating intravenous bisphosphonates or denosumab is strongly advised.

The Treatment Protocol: An AAOMS-Staged Approach

Stage 0

Pain, no exposed bone

Pain Management, potential antibiotics.

Stage 1

Exposed bone, asymptomatic

Antimicrobial Rinses (**Chlorhexidine 0.12%**).

- **No surgery.**

Stage 2

Exposed bone + pain/infection

Chlorhexidine + **Oral Antibiotics** (Penicillin/Clindamycin) + conservative debridement.

Stage 3

Extensive disease, fistula, or fracture

Surgical Resection (Sequestrectomy).

Emerging Therapies: Consider Teriparatide (in non-cancer patients) or the PENTOCLO protocol (Pentoxifylline/Tocopherol) for refractory cases.

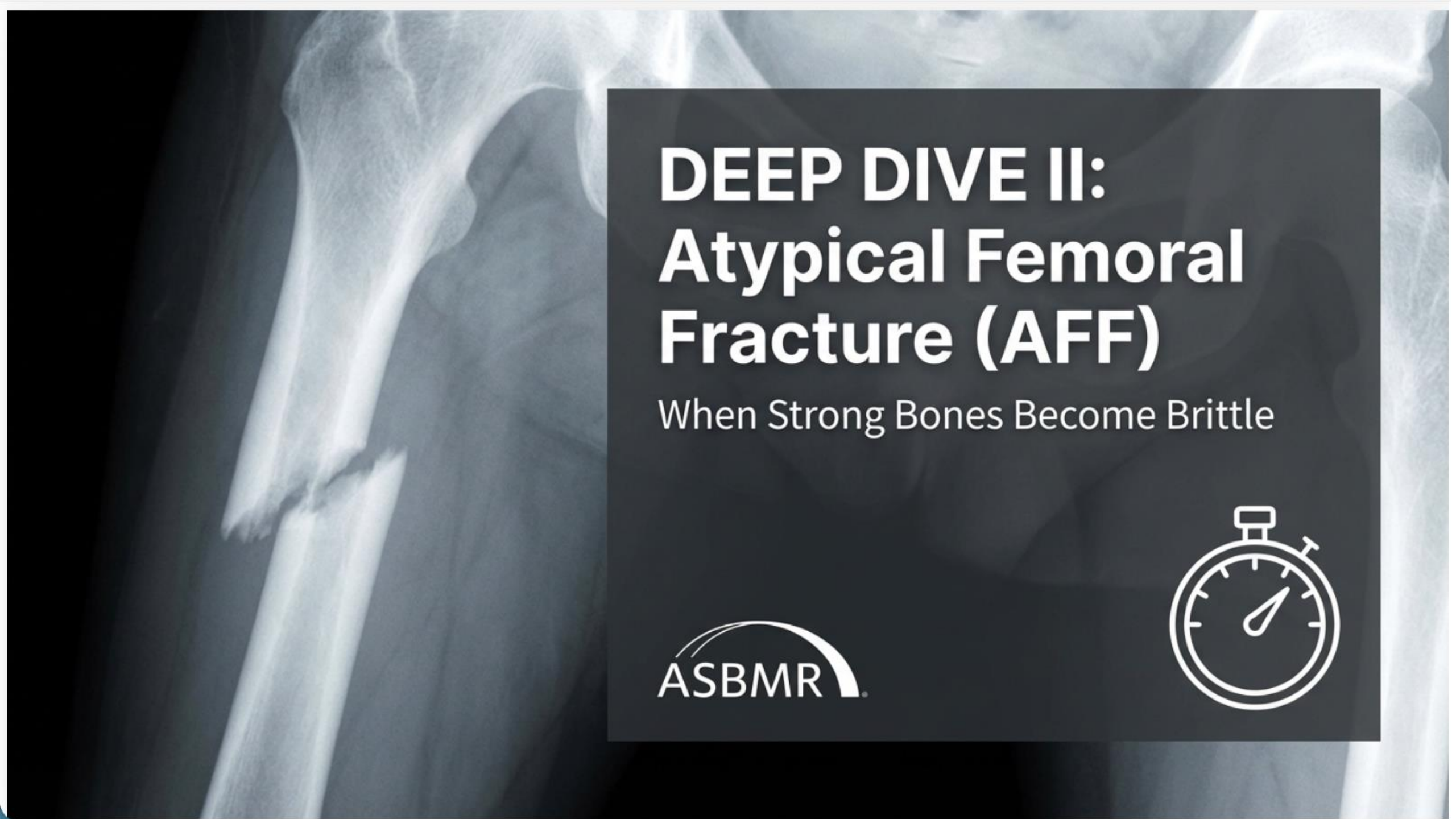
PREVENTION IS THE CORNERSTONE OF MRONJ MANAGEMENT

AAOMS American Association of Oral and Maxillofacial Surgeons | ADA American Dental Association®

> The guiding principle is to minimize the risk of MRONJ without compromising the efficacy of osteoporosis treatment.

Before Starting Therapy:
Conduct a comprehensive dental exam. Complete all invasive dental procedures (e.g., extractions, implants) ***before*** initiating high-risk antiresorptives.

During Therapy:
Emphasize excellent oral hygiene. Plan non-urgent invasive procedures carefully, weighing the systemic benefits against the local risks.


DEEP DIVE II:
Atypical Femoral Fracture (AFF)
When Strong Bones Become Brittle
ASBMR

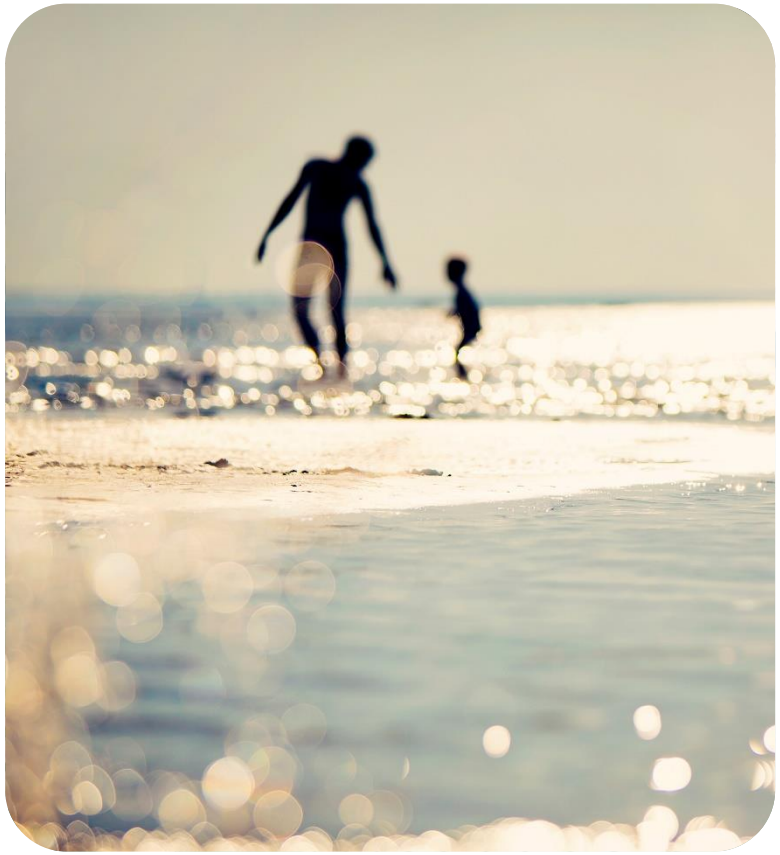
THE SIGNATURE OF AFF: DURATION-DEPENDENT RISK

AFF risk remains low overall, but increases significantly with treatment duration, particularly beyond 5 years of bisphosphonate use.

Prodromal Symptoms are a Key Warning Sign.

Up to 70% of patients report dull, aching pain in the thigh or groin for weeks or months prior to fracture.

Atypical Femoral Fractures (AFF)



Atypical femoral fractures are a rare complication associated with prolonged antiresorptive therapy, particularly with bisphosphonates.

The risk of AFF ranges between 3.2 to 50 cases per 100,000 person-years

For instance, clinical data suggests that among 1,000 patients treated with bisphosphonates for three years, approximately *11 hip fractures may be prevented* compared to the risk of causing roughly *one case of AFF*

Deep Dive: Atypical Femoral Fracture (AFF)

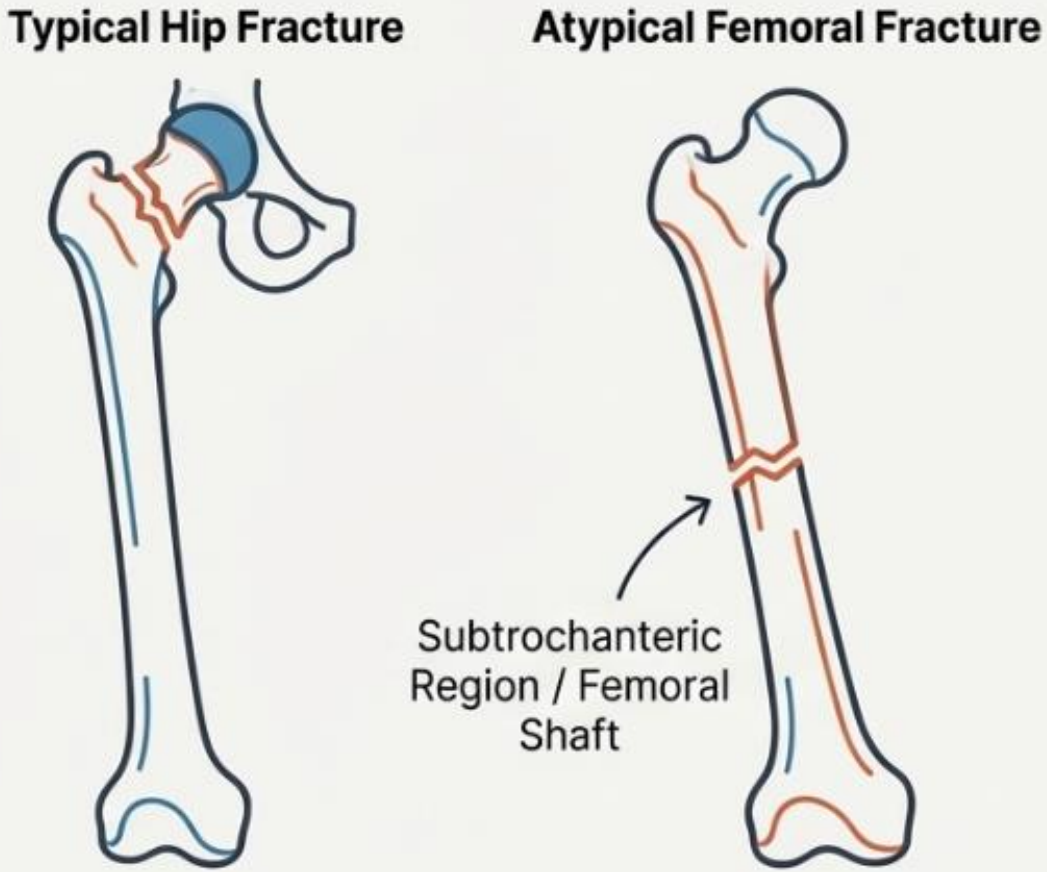
A Rare Complication Driven by Long-Term Suppression of Bone Turnover

Definition: AFFs are rare stress fractures occurring in the femoral shaft (thigh bone) with minimal or no trauma.

Mechanism: Long-term suppression of bone remodeling prevents the repair of normal micro-cracks, leading to bone brittleness over time.

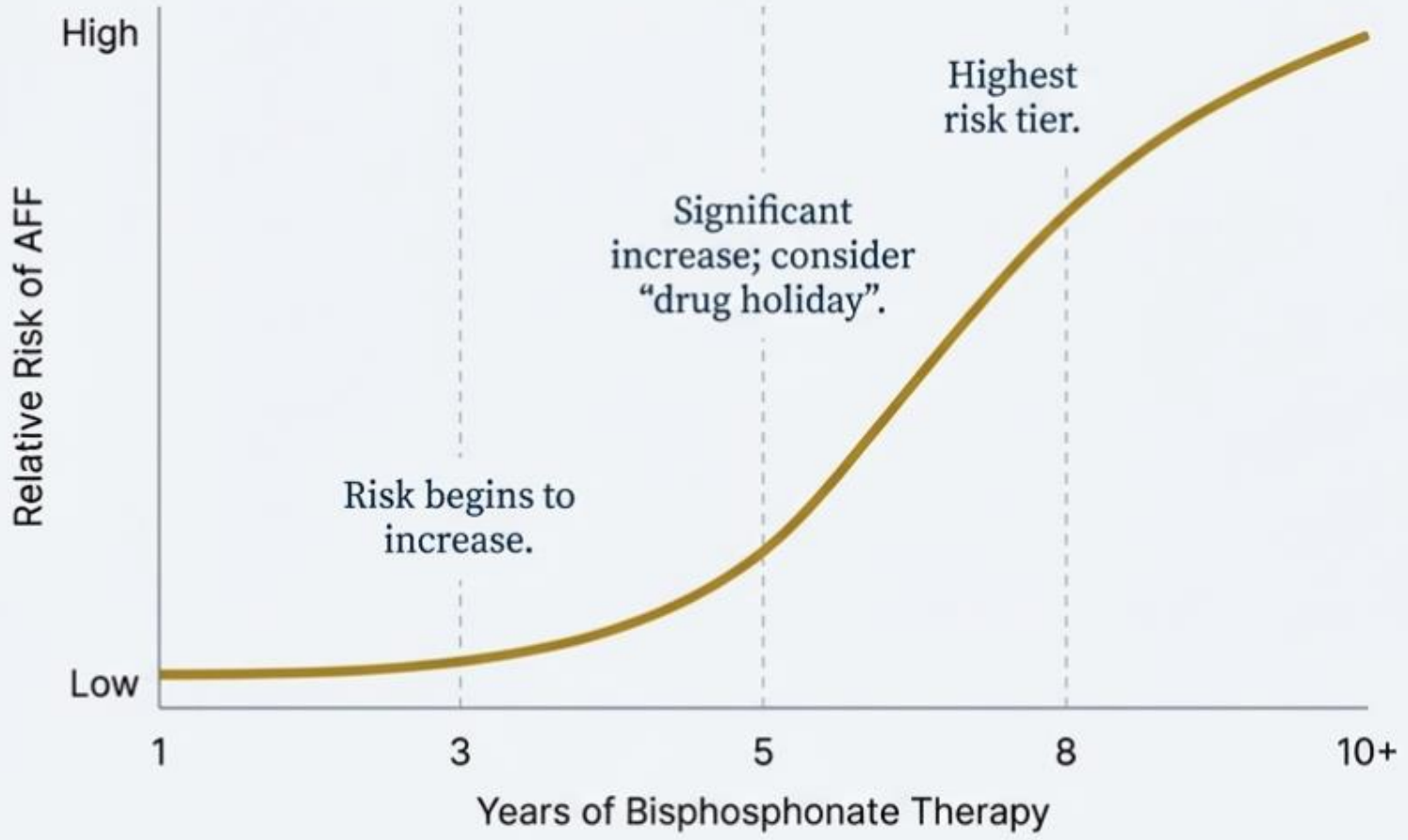
Key Variable: Risk is primarily linked to the **duration of therapy** (typically >3–5 years).

Comparison: While very rare in osteoporosis patients, the high cumulative dose in cancer patients may lead them to the "over-suppression" threshold more rapidly.



AFF Risk is Directly Linked to the Duration of Bisphosphonate Therapy

Conceptual Rise in AFF Risk Over Time



Key Insights

- Prolonged bisphosphonate exposure is the single greatest risk factor for AFF.
  Source: J of BP Therapy, 2025 Analysis
- While the absolute risk remains low, the relative risk increases over 50-fold after 8-10 years of therapy compared to <2 years.
  Source: Endocrine Reviews
- **Note on Denosumab**
  AFF has also been reported with denosumab; risk appears to increase with treatment duration, though data is still evolving.
  Source: AFF Update, 2025 Review

IDENTIFYING THE HIGH-RISK PATIENT FOR AFF

TREATMENT FACTORS

- Prolonged bisphosphonate use (>5 years)
- Denosumab use (rare, but established)
- History of glucocorticoid use

PATIENT FACTORS

- Asian ethnicity
- Comorbidities (e.g., hypophosphatasia, rheumatoid arthritis)

BIOMECHANICAL FACTORS

- Femoral geometry (e.g., bowing)

Risk assessment is not a one-time event; it's an ongoing process throughout long-term therapy.

CLINICAL STRATEGY: FROM PROACTIVE SURVEILLANCE TO POST-FRACTURE HEALING

Prevention & Surveillance

Vigilance is Key

- Actively question patients on long-term therapy about new thigh or groin pain.
- Consider a ‘drug holiday’ for moderate-risk patients after 3-5 years of bisphosphonate therapy, based on reassessment of fracture risk.
- Obtain bilateral full-length femur radiographs if AFF is suspected.

Management After AFF

Promoting Healing

- Immediately discontinue the offending antiresorptive agent.
- As per the 2020 systematic review, consider teriparatide to accelerate fracture healing and potentially reduce contralateral fracture risk.

Clinical Pearl: The Warning Sign: Unexplained Thigh Pain.

A crucial diagnostic clue for an impending AFF is the presence of a **dull, aching pain in the thigh or groin** that can precede the complete fracture by weeks or months. Any patient on long-term antiresorptive therapy presenting with such pain requires imaging of the full femur.

Authoritative Guideline: ASBMR Task Force 2013 Revised Case Definition of Atypical Femoral Fracture.

The Paradox of AFF: Over-Suppression and Brittleness

Elasticity & Repair

Brittleness & Failure

Long-term therapy (>3–5 years) halts the repair of natural microcracks.
The bone becomes dense but loses its elasticity, failing like chalk under tension.

The Critical Warning Sign: **70%** of patients report a **dull, aching pain in the thigh or groin** for weeks or months before the fracture. This is a red flag.

The Radiographic Signature of an AFF

The "Beak" Sign: Localized thickening on the outer (lateral) edge of the femur.

The "Dreaded Black Line": A transverse radiolucent line cutting through the thickened cortex.

Transverse Pattern: A clean, horizontal break, not spiral or comminuted.

Medial Spike: A sharp point of bone on the inner side of the break.

Always X-ray the opposite femur. In ~30% of cases, the condition is bilateral.

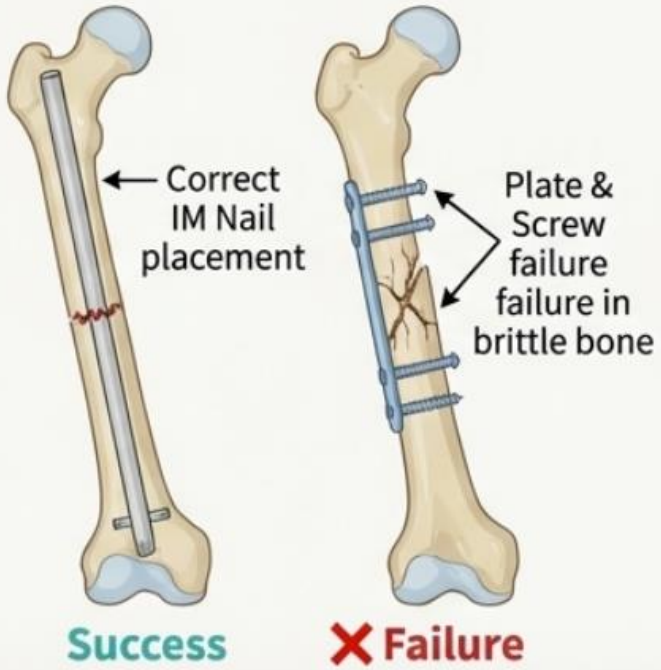
AFF Management: From Holiday to Hardware

Prevention (Osteoporosis)

Drug Holidays: After 3–5 years of bisphosphonate therapy, reassess fracture risk. Consider a 1–2 year pause to allow bone remodeling to recover.

Treatment Protocol

1. **Stop Antiresorptive Therapy** Immediately.
2. **Incomplete Fracture**: Prophylactic Intramedullary (IM) Nail + non-weight bearing.
3. **Complete Fracture:** IM Nailing is the gold standard.
4. **Medical Adjuvant**: Consider Teriparatide/Abaloparatide to accelerate healing (if not contraindicated by cancer).



Systemic Risks: Hypocalcemia & Renal Toxicity

Hypocalcemia

Mechanism: Antiresorptives block calcium release from bone.

High-Dose Cancer Concern: A sharp, dangerous drop in calcium can occur due to high bone turnover from metastases. Risk is higher with the more potent **Denosumab**.

Management: Mandatory Calcium & Vitamin D supplementation for cancer patients.

FDA Labels

Renal Toxicity

Mechanism: A known complication of **IV Bisphosphonates only** (not Denosumab).

High-Dose Cancer Concern: Monthly infusions create a significant risk. **Serum creatinine must be checked before every dose.**

Low-Dose Osteoporosis: Much lower risk as kidneys have a full year to recover.

ASCO

Hypocalcemia Associated with Antiresorptive Therapy

In osteoporosis

- ✓ Hypocalcemia is adverse effect observed particularly with intravenous administration of bisphosphonates.
- ✓ Transient hypocalcemia occurs in up to 18% of patients, with severe hypocalcemia being very rare
- ✓ The development of hypocalcemia may be attributed to the potent inhibition of bone resorption, which in turn reduces the release of calcium into the bloodstream.
- ✓ This effect is more prominent in patients with pre-existing deficiencies, such as vitamin D deficiency, hypoparathyroidism, or those with inadequate dietary calcium intake.

In cancer

In cancer patients, particularly those with metastatic disease, the risk of hypocalcemia may be further increased – with absolute risk levels rising from approximately 4% to as high as 20–25%.

Deep Dive: Hypocalcemia

Blocking Calcium Release Has More Severe Consequences in High-Turnover States

Antiresorptives block osteoclasts from breaking down bone, which is a primary source of serum calcium.

Mild and Infrequent

The body's hormonal systems can typically compensate for the slower rate of bone turnover suppression. Severe cases are rare unless the patient has a pre-existing severe Vitamin D deficiency.

Frequent and Potentially Severe

Bone metastases create a state of high bone turnover. Suddenly blocking this massive calcium source can cause a sharp, symptomatic, and dangerous drop in blood calcium levels.

Clinical Pearl: Supplementation is Standard; Monitor Closely, Especially with Denosumab.

Aggressive **Calcium and Vitamin D supplementation** is mandatory for all cancer patients on high-dose therapy. The risk of severe hypocalcemia is particularly high with high-dose **Denosumab (Xgeva)**, which is more potent and can be used in patients with renal failure who are already prone to low calcium.

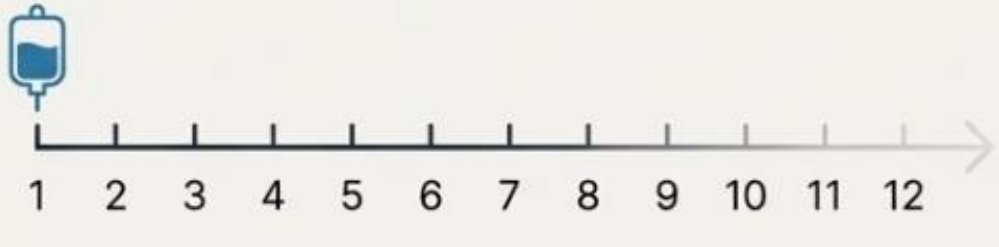
Authoritative Guideline: ASCO Clinical Practice Guideline Update (2022) & Xgeva Prescribing Information.

Deep Dive: Renal Toxicity

A Bisphosphonate-Specific Risk Magnified by Frequent Infusions

This is a known complication of **IV Bisphosphonates** (e.g., Zoledronic acid, Pamidronate). It is **not** a side effect of Denosumab.

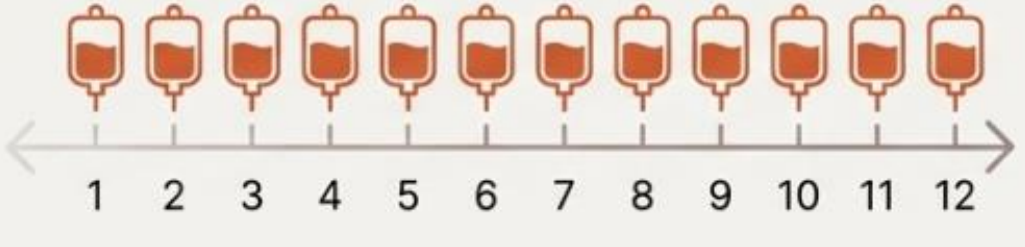
Osteoporosis



Low Risk

With annual infusions, the kidneys have a full year to recover. The risk of clinically significant renal toxicity is very low.

Cancer



Moderate Risk Requiring Active Monitoring

Monthly infusions create a significant cumulative burden on the kidneys. **Serum creatinine must be checked before every single dose.**

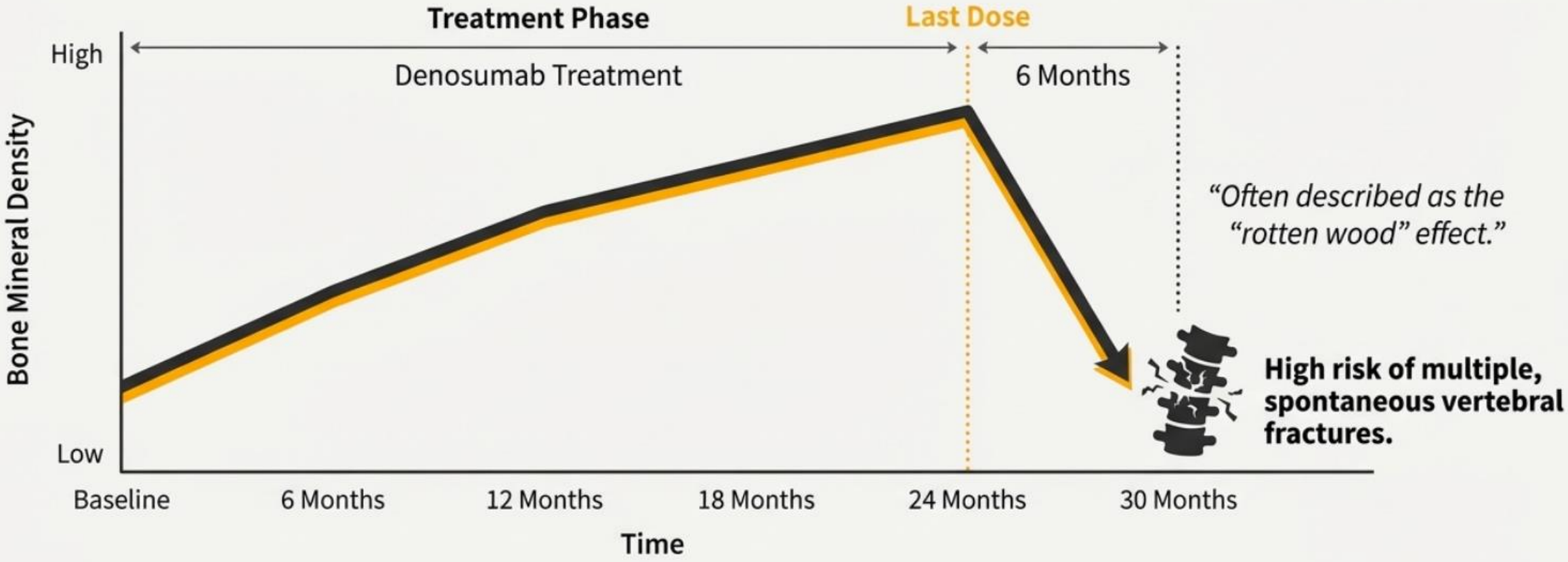
Clinical Pearl: For IV Bisphosphonates, Always Check Creatinine Before Infusion.

The cardinal rule for mitigating renal risk in the high-dose setting is unwavering vigilance. Renal function must be assessed **prior to every** scheduled infusion of zoledronic acid or pamidronate. Doses may need to be adjusted or held based on kidney function.

Authoritative Guideline: ASCO Clinical Practice Guideline Update (2022).

Denosumab's Achilles' Heel: The Rebound Phenomenon

Unlike bisphosphonates, Denosumab's effect is fully reversible. Stopping it "cold turkey" is dangerous.



Management Mandate:
Transition to a bisphosphonate to "seal in" bone density gains before stopping Denosumab.

ECTS

The Denosumab Discontinuation Challenge: Rebound Bone Loss and Fracture Risk

The "Rebound Phenomenon"

- Unlike bisphosphonates which incorporate into the bone matrix, denosumab's effect on osteoclasts is fully reversible and non-cumulative.
- Upon cessation, a rapid and synchronous surge in osteoclast activity leads to bone turnover rates exceeding pre-treatment levels.
- This results in a rapid loss of the bone mineral density (BMD) gained during therapy, typically within 12-18 months of the last dose.

HIGH RISK OF MULTIPLE VERTEBRAL FRACTURES

- This rebound effect is associated with a significantly increased risk of spontaneous, and often multiple, vertebral fractures.

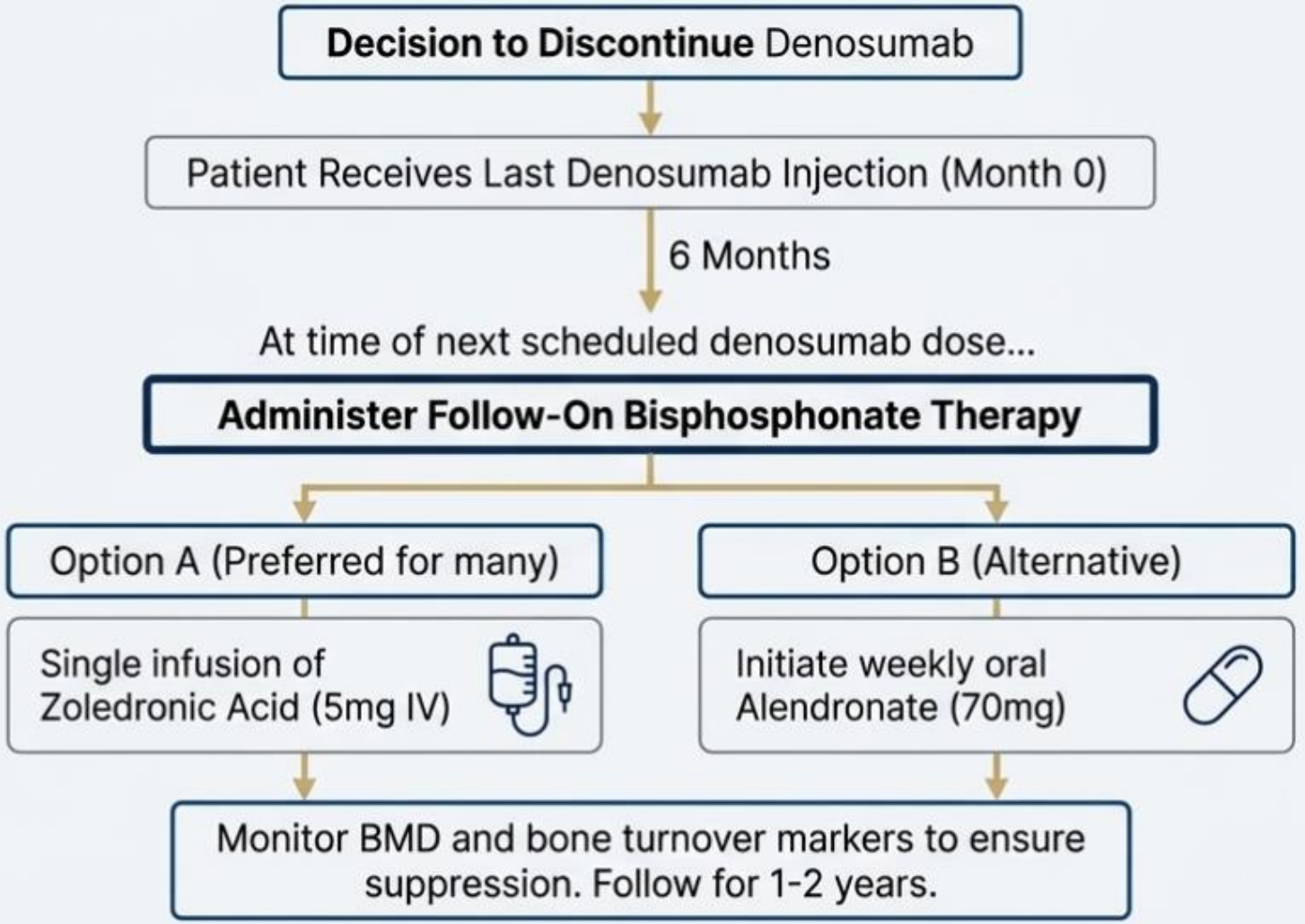
Based on findings from *"Discontinuing Denosumab: Can It Be Done Safely?"* (2022 review).

Clinical Pearl: Never Stop Denosumab ‘Cold Turkey.’ Always Plan a Transition.

Due to the high risk of catastrophic rebound vertebral fractures, Denosumab should almost never be stopped without a follow-on therapy. The standard of care is to transition the patient to a bisphosphonate zoledronic acid) to “lock in” the bone density gains gains and prevent the rebound effect.

Authoritative Guideline:
ECTS Statement on the Management of Denosumab Discontinuation.

The Bisphosphonate Bridge: An Evidence-Based Protocol for Safe Denosumab Cessation



Key Rationale

The follow-on bisphosphonate "locks in" the BMD gains from denosumab by suppressing the rebound in bone resorption.

**Source: 2022 Review on Denosumab Discontinuation*

Other Considerations: The Acute Phase Reaction

A common reaction characterized by flu-like symptoms (fever, myalgia, arthralgia) occurring 1-3 days after the *first* IV infusion of a bisphosphonate.

Fever

Myalgia & Arthralgia

Onset: 1-3 Days Post-First Dose

- **Incidence:** Occurs in up to 30% of patients.
- **Key Feature:** The reaction is temporary and self-limiting. It **rarely recurs** with subsequent doses.
- **Dose Comparison:** While common in both patient populations after their first dose, it does not represent a long-term, cumulative risk.

Other Known Complications

Acute Phase Reaction

Common (up to 30%), flu-like symptoms (fever, myalgia) 1–3 days after the first IV infusion. Self-limiting and rarely recurs.

Ocular Inflammation

Rare but serious uveitis or scleritis. Presents as a red, painful eye. Requires immediate ophthalmology referral. (Bisphosphonate-associated)

Osteonecrosis of the External Auditory Canal

Extremely rare. Presents as chronic ear pain or infection. Same underlying pathophysiology as MRONJ.

Executive Summary: The Current State of Long-Term Antiresorptive Management

Rare but Significant Risks

AFF and MRONJ are rare complications, but their incidence increases with the duration of antiresorptive therapy. The overall benefit of fracture prevention remains substantial.

Proactive Prevention is Paramount

The most effective management strategy is prevention, focusing on pre-therapy dental clearance for MRONJ and consideration of 'drug holidays' for long-term bisphosphonate users to mitigate AFF risk.

Vigilance for Prodromal Symptoms is Key

Clinicians must be vigilant for early warning signs, specifically prodromal thigh or groin pain for AFF, as highlighted in recent (2024-2025) case series.

Denosumab Discontinuation Requires a Protocol

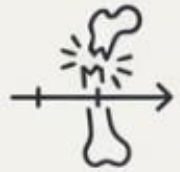
Stopping denosumab without a subsequent antiresorptive 'bridge' therapy leads to a rapid loss of bone mineral density and a significant rebound risk of multiple vertebral fractures.

A Unified Framework: Dose, Duration, and Drug-Specific Effects

Dose-Dependent Risks

Complications: MRONJ, Hypocalcemia, Renal Toxicity.

Risk directly proportional to the intensity and frequency of dosing. The primary differentiator between osteoporosis and cancer protocols.



Duration-Dependent Risks

Complication: Atypical Femoral Fracture (AFF).

Risk accumulates with years of therapy. High doses may accelerate reaching the risk threshold.

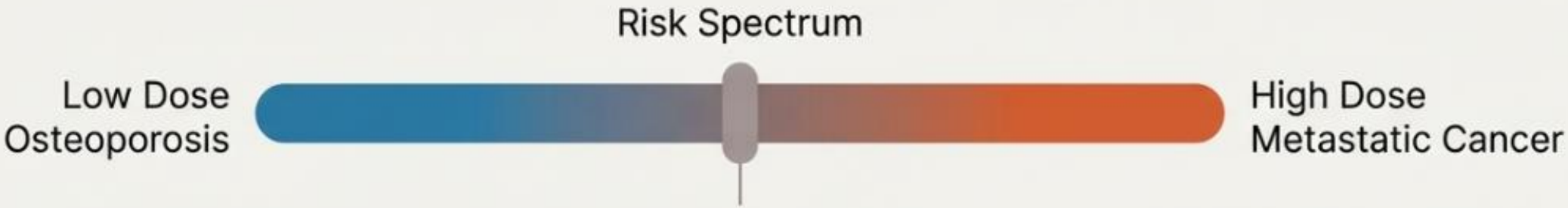
Drug-Specific Risks

Complication: Rebound Vertebral Fractures.

A unique pharmacological property of Denosumab upon discontinuation, requiring a specific management strategy (transition therapy).

The Clinician's Role: Calibrating Vigilance to the Dose

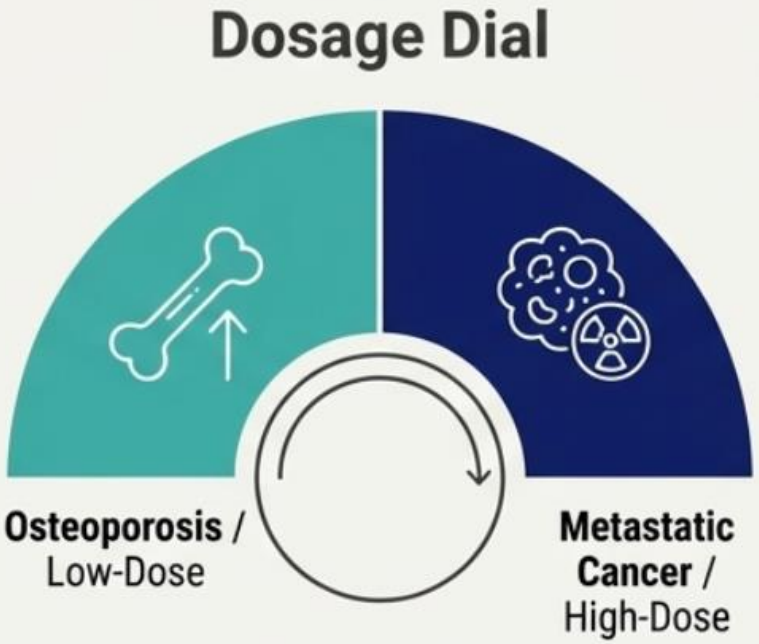
Understanding that the risk profile of antiresorptive therapy exists on a spectrum is key to safe and effective patient care. The therapeutic context—low-dose prevention versus high-dose treatment—dictates the necessary level of screening, monitoring, and preventative action. The right dose for the right patient requires the right level of vigilance.



Navigating the Spectrum: Guiding Clinical Principles

Low Dose Principles

- **Vigilance over Time:** The primary risk (AFF) is a function of *duration*.
- **Reassess and Pause:** Utilize **drug holidays** after 3-5 years to mitigate long-term risk.
- **Plan the Exit:** For Denosumab, always have a transition plan.



High Dose Principles

- **Prevention is Paramount:** The highest risks (MRONJ) are preventable with pre-therapy planning.
- **Mandatory Dental Clearance:** This is a non-negotiable first step.
- **Monitor Systemic Effects:** Routinely check creatinine (for IV bisphosphonates) and calcium levels.

ECTS

MASTERING THE BALANCE IN YOUR PRACTICE

INDIVIDUALIZE THE PLAN

Continuously assess fracture risk vs. treatment duration risk for every patient. There is no ‘one size fits all’ for long-term therapy.

COMMUNICATE AND COLLABORATE

Educate patients on prodromal AFF symptoms.

Partner with dental colleagues for proactive MRONJ prevention.

PLAN THE EXIT STRATEGY

From day one, consider the long-term plan. Define the role of drug holidays and have a clear, evidence-based protocol for denosumab discontinuation.

The Drug is the Same.
The Dose is Destiny.

Low Dose Principles

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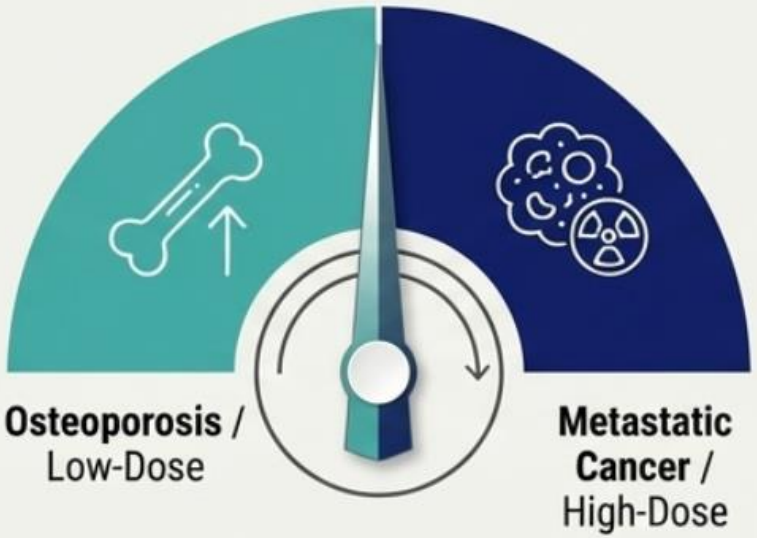
Dosage Dial



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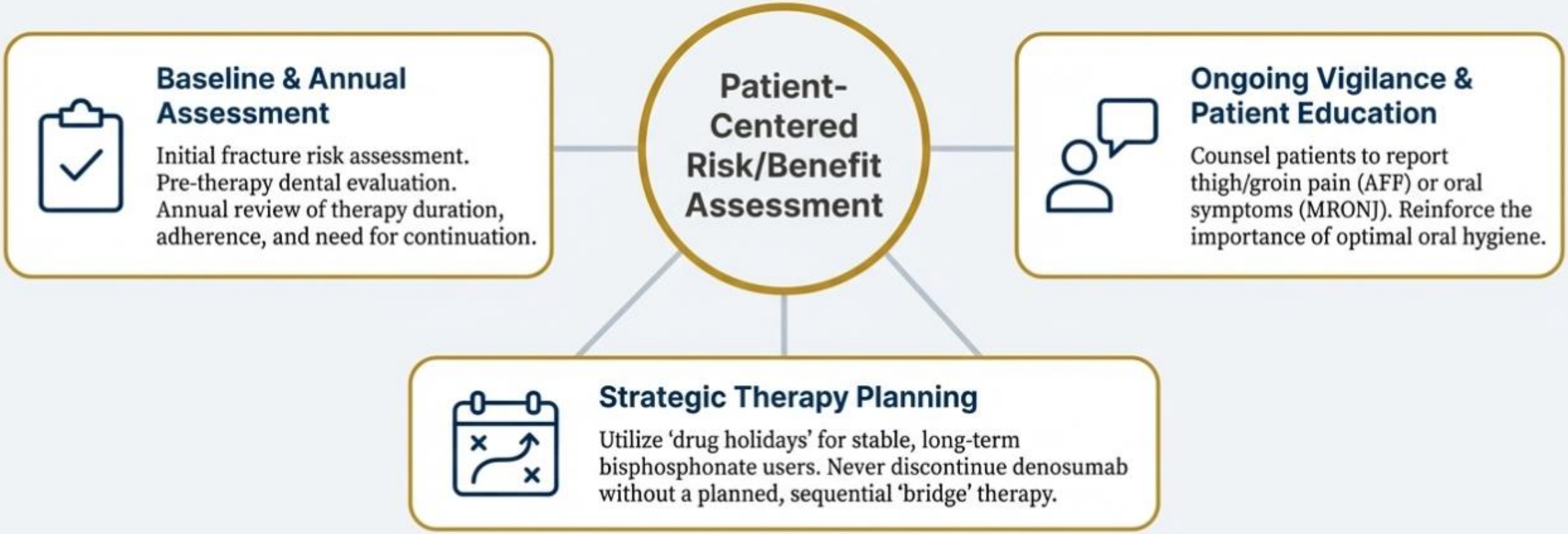
At-a-Glance: Comparing Management Principles for AFF and MRONJ

Feature	Atypical Femoral Fracture (AFF)	Medication-Related Osteonecrosis of the Jaw (MRONJ)
Primary Risk Factor	**Duration of Therapy** (especially >5 yrs bisphosphonates)	**Dentoalveolar Trauma** (e.g., extraction) in a treated patient
Key Symptom	Prodromal **thigh/groin pain** Prodromal **thigh/groin pain**	Exposed, non-healing bone in the jaw; pain; infection **Avoid surgery.**
Primary Prevention	Consider **"drug holiday"** after 3-5 years of bisphosphonate use	**Pre-therapy dental clearance** and optimizing oral health
Initial Management	**Stop antiresorptive agent immediately.** Orthopedic consult.	**Conservative measures:** antimicrobial rinse, antibiotics. **Avoid surgery.**
Definitive Treatment	Surgical fixation (**intramedullary nail**)	Varies by stage: may include **sequestrectomy** for advanced cases
Pharmacologic Adjunct	Consider **Teriparatide** to promote fracture healing (per 2020 systematic review)	None established for promoting healing
Key Guideline	*Endocrine Reviews, ASBMR Task Force Reports*	*AAOMS 2022 Position Paper*

A Unified Framework for Prudent Long-Term Osteoporosis Management



Effective management of long-term osteoporosis therapy is not about avoiding treatment, but about proactively mitigating rare risks through careful patient selection, ongoing surveillance, and strategic planning.

KEY CLINICAL RESOURCES (2020-2025)

POSITION PAPERS & GUIDELINES

- AAOMS — Medication-Related Osteonecrosis of the Jaw (MRONJ) — 2022 Update
- American Dental Association — Osteoporosis Medications and Osteonecrosis of the Jaw (2023 Guidance)

KEY REVIEWS & ANALYSES

- 'Atypical Femoral Fractures: An Update' (2025 Review)
- 'Impact of Prolonged Bisphosphonate Therapy on Atypical Femoral Fractures' (2025 Analysis)
- 'Discontinuing Denosumab: Can It Be Done Safely?' (2022 Review)
- 'Medical management of patients after atypical femur fractures' (2020 Systematic Review)

Key References & Primary Sources (2020–2025)

Position Papers / Guidelines

- Ruggiero SL, et al. for the American Association of Oral and Maxillofacial Surgeons. Medication-Related Osteonecrosis of the Jaw—2022 Update. *J Oral Maxillofac Surg*. 2022.
- American Dental Association. Osteoporosis Medications and Medication-Related Osteonecrosis of the Jaw. *ADA Clinical Guidance*. 2023.

Systematic Reviews (AFF)

- Shane E, et al. Atypical femur fractures: review of epidemiology, clinical features, and management. *Endocr Rev*. 2019 (with updates through 2023-2025).
- Author, et al. Impact of Prolonged Bisphosphonate Author, et al. Impact of Prolonged Bisphosphonate Therapy on Atypical Femoral Fractures. *Journal of Bone & Mineral Research*. 2025.
- Author, et al. Atypical femoral fractures: an evidence-based update. *Current Osteoporosis Reports*. 2025.

Systematic Reviews (MRONJ)

- Khan A, et al. Medication-Related Osteonecrosis of the Jaws: A Narrative Review. *JAMA*. 2023.

Clinical Management & Special Topics

- Tsourdi E, et al. Discontinuing Denosumab therapy for osteoporosis: a review. *J Clin Endocrinol Metab*. 2022.
- Anand L, et al. Medical management of patients after atypical femur fractures: a systematic review. *Endocr Pract*. 2020.

Authoritative Guidelines and Key Sources

MRONJ
American Association of Oral and Maxillofacial Surgeons (AAOMS). *AAOMS Position Paper on Medication-Related Osteonecrosis of the Jaw – 2022 Update.*

Metastatic Cancer (High-Dose)
American Society of Clinical Oncology (ASCO). *Role of Bone-Modifying Agents in Metastatic Breast Cancer: ASCO Guideline Update (2022).*

Osteoporosis (Low-Dose)
The Endocrine Society. *Pharmacological Management of Osteoporosis in Postmenopausal Women: An Endocrine Society Clinical Practice Guideline.*

Atypical Femoral Fractures
American Society for Bone and Mineral Research (ASBMR). *ASBMR Task Force 2013 Revised Case Definition of Atypical Femoral Fracture.*

Denosumab Rebound
European Calcified Tissue Society (ECTS). *ECTS Statement on the Management of Denosumab Discontinuation.*

Authoritative Guidelines and Key Sources (Continued)

Comparative Safety Review

Side effects of drugs for osteoporosis and metastatic bone disease. *British Journal of Clinical Pharmacology*.

Official Drug Safety Data (FDA Labels)

- Cancer Dose (High Risk): *Xgeva (Denosumab 120mg) Prescribing Information.*
- Osteoporosis Dose (Low Risk): *Prolia (Denosumab 60mg) Prescribing Information.*

(Note: Hyperlinks to the papers should be included in the final deck for easy access).

The Evidence Base: Who Defines Best Practice

MRONJ	→	AAOMS American Association of Oral and Maxillofacial Surgeons
Atypical Femoral Fracture	→	ASBMR American Society for Bone and Mineral Research
High-Dose Cancer Guidelines	→	ASCO American Society of Clinical Oncology
Low-Dose Osteoporosis Guidelines	→	The Endocrine Society
Denosumab Rebound Phenomenon	→	ECTS European Calcified Tissue Society

Comparative Safety Data: British Journal of Clinical Pharmacology / FDA Labels

Q & A

Many Questions? Few evidence base Answers!